

**Comments on the Proposed Report on Carcinogens Review Process**  
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In 76FR68461 (November 4, 2011), comments were requested from the public on the National Toxicology Program (NTP) Proposed Report on the Carcinogens Review Process in preparation for a public discussion at the December 15, 2011 NTP Board of Scientific Councilors meeting. I am pleased to submit the following written comments, which reflect my own opinions, though they were produced with support from the Styrene Information and Research Center.

I am Lorenz Rhomberg, Ph.D., FATS, a Principal at Gradient, an environmental consulting firm that provides risk assessment and toxicological expertise to a variety of clients in the public and private sectors. I have commented on the proposed listing of particular chemicals in the Report on Carcinogens (RoC), but my present comments focus on the general process of considering listing of chemicals in the RoC rather than on any specific chemical's listing. In my career, I have been a government (US EPA) and academic (Harvard School of Public Health) risk assessor, and a consultant (Gradient). I have served on several committees organized by the National Research Council on risk assessment topics and, especially in recent years, I have been a public proponent of a more structured approach to conducting weight-of-evidence evaluations regarding the potential for particular chemicals to affect human health. My comments are informed by this experience.

In general, it is to be appreciated that the NTP is undertaking the examination of its review process for listing proposals. This is a good and appropriate development that recognizes the evolution and maturation of the larger questions in the field about how chemical hazards can be identified and characterized. The solicitation for comments from the public is appropriate and appreciated.

A credible and respected listing process for the Report on Carcinogens (RoC) is extremely important. While the RoC itself is not a regulatory document, it is used by many agencies to determine appropriate regulations for a wide variety of substances. For this reason, the process must be careful and thorough, and include an analysis of all available information for each particular substance under review.

The credibility of the listing review process has two important components that need to be addressed. The first is the credibility of PROCESS, that is, the procedures that are followed to ensure a thorough, thoughtful, and unbiased review procedure that ensures inclusion of the appropriate and relevant information, recruits informed reviewers with needed expertise, identifies and analyzes the issues

that may exist in the evaluation and application of that information, and provides a public and transparent process for coming to judgments.

The second critical component is the credibility of JUDGMENTS, that is, the scientific soundness and acceptance by the broader scientific community of the criteria for listings and for weight-of-evidence characterizations, with sufficiently developed standards such that individual decisions are not seen as arbitrary or based on views of the selected reviewers, but rather represent sound reasoning and well justified conclusions that would be endorsable by scientists generally.

The proposed changes in the listing process principally address the first of these factors—the process itself. There are significant improvements in the proposed changes, notably, a broader basis for the ability of interested parties to call for reviews or revisions of existing listings. There are, however, some systemic difficulties that still need to be addressed—issues that have raised concerns in previous practice. A truly credible process needs to address how the members of the reviewing Board of Scientific Counselors (BSC) are chosen. It needs to ensure appropriate expertise and it needs to make sure that a sufficiently broad set of reviewers represent the span of informed and reasoned opinion on the matters under review. In addition, there have been concerns in the past about the thoroughness of exploration of issues of interpretation, about the sufficiency of time devoted to exploring these issues and presenting the full questions to the BSC itself rather than passing on just a summary, and about the reliance on scientists whose work is under review to present the overview of their work and others work to the Board. The review process must be designed to provide sufficient time for thorough reviews and opportunities to comment, by both interagency and public reviewers, so that the public can see that the BSC is making its decisions in full awareness of the underlying issues and the full span of pertinent and informative data.

Although steps to address the credibility of process are crucial, they are not by themselves sufficient to ensure that reviews are seen as well reasoned and defensible. The second credibility factor, judgment, is crucial. There must be an established set of criteria by which all relevant data for a particular substance is analyzed in order to justify its inclusion in the RoC. This necessarily entails a real weight-of-evidence analysis that satisfies the following considerations:

- Accounts for contradictory or inconsistent data
- Weighs negative as well as positive studies
- Examines biological and mechanistic plausibility of study results, not just accepting their outcomes at face value

The call for establishing weight-of-evidence methods is in accord with accepted practice in many other agencies [see for example the recent National Academy of Sciences formaldehyde review, US EPA's proposed revisions to the Integrated Risk Information System (IRIS) assessments, and the recent Clean Air Scientific Advisory Committee pronouncements]. Weight-of-evidence analysis as an integral part of the RoC listing process will ensure a more accurate listing of substances that may pose a hazard to human health by virtue of their carcinogenicity.

In conclusion, the credibility and wide acceptance of the RoC listing process requires both the articulation and application of a sound set of inference principles through which supportable scientific judgments can be made and an open, transparent, objective, and inclusive process of discussion and evaluation of evidence through which these criteria can be applied. The current Proposed Report on the Carcinogen Review Process, while providing a promising start, is construed too narrowly, and focuses too much on selected elements of process alone at the expense of weight-of-evidence principals, to provide the needed rethinking of the RoC listing process. I urge the BSC to make broadening and deepening this revision process a priority.